

The Challenge of Managing Wheezing in Infants

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Around the world, thousands of times a day, an infant 6 to 8 months old with a runny nose, a cough, and wheezing arrives in a pediatrician's office or an outpatient clinic. In Western countries about one in three children has at least one episode of wheezing before his or her third birthday.¹ Even with all these wheezy children, we still do not know the answers to a number of basic questions. What is the cause and type of the wheezing illness in an individual child? What does it portend for the future of this child? How should it be treated?

A first episode of wheezing is usually triggered by a viral infection. If respiratory distress occurs along with this episode, the condition is labeled bronchiolitis. The diagnosis is even firmer if there is also evidence of infection with respiratory syncytial virus (RSV). In many children, a first episode is followed by more symptoms. Based on the occurrence of symptoms, two general patterns of wheezing can be distinguished: episodic and unremitting wheeze (Fig. 1). Episodic wheezing is defined as wheezing in discrete episodes of 2 to 4 weeks in duration, with the child being well in between episodes.² The trigger is usually a viral infection. In unremitting wheezing, the child has distinct episodes of wheezing but between these severe episodes also has intermittent symptoms, such as coughing or wheezing at night or in response to exercise, crying, laughter, mist, or cold air. Viral infections are also the most common causes of these severe episodes, but they may persist in the presence of other triggers, such as passive smoking, allergen exposure, or air pollution. Consequently, this wheezing phenotype has also been termed multitrigger wheezing.² The wheezing phenotypes can sometimes be hard to distinguish and can change as children grow older: episodic wheezing may give way to unremitting wheezing and vice versa, depending on environmental exposures and stages of development.³

Episodic wheezing is usually not associated with atopy and rarely progresses to asthma. In contrast, unremitting wheezing in children of preschool age is often associated with atopic sensitization as early as the first year of life. These

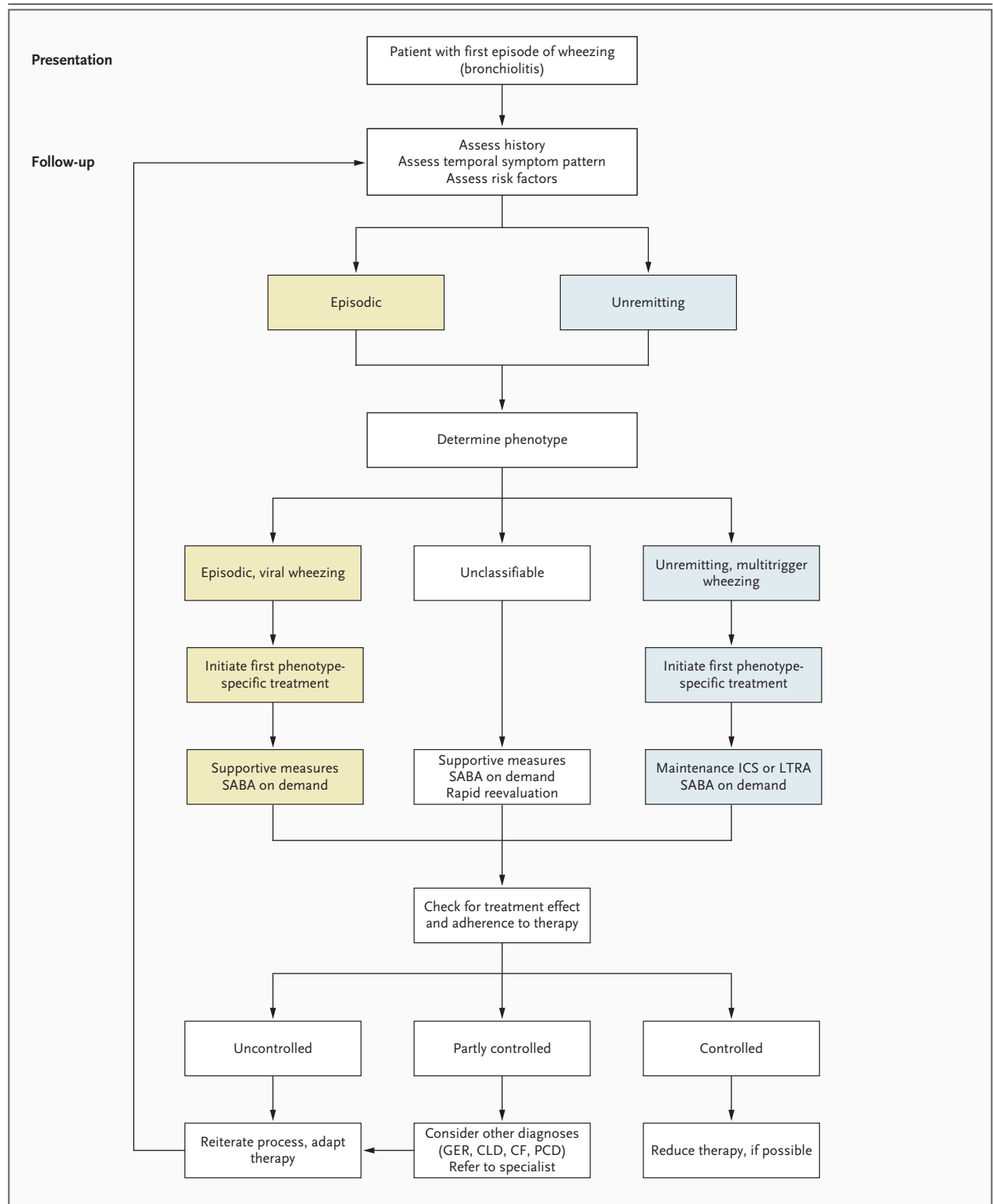
Figure 1 (facing page). Management of Preschool Wheezing Disorders.

The key components of a flexible management approach to preschool wheezing are phenotype assessment; monitoring of the disease process, treatment, and compliance; and adaptation of treatment over the course of the illness. Bronchiolitis refers to a first episode of wheezing, with respiratory distress triggered by a viral infection. Episodic wheezing refers to discrete episodes of wheezing without intermittent symptoms. Unremitting wheezing refers to distinct episodes of wheezing with intermittent symptoms, such as coughing or wheezing at night or in response to exercise, crying, laughter, mist, or cold air. CF denotes cystic fibrosis, CLD chronic lung disease, GER gastroesophageal reflux, ICS inhaled corticosteroids, LTRA leukotriene-receptor antagonists, PCD primary ciliary dyskinesia, and SABA short-acting beta-agonists.

children often have allergies to foods such as hen's eggs and cow's milk. Many of these children have atopic dermatitis or sensitization to indoor allergens, with subsequent development of impaired lung function.¹ By the time they are in school, we call their disease asthma. It is the progression from episodic to unremitting and atopic wheezing that allows such classification — not the clinical presentation at the first episode.

If it were only that simple. Unremitting wheezing may also occur after the development of RSV-induced bronchiolitis and has also been associated with early and repetitive rhinovirus infections.⁴ Environmental exposures affecting airway growth, such as prenatal exposure to tobacco smoke and environmental air pollution, are associated with decreased postnatal lung function^{5,6} and with unremitting preschool wheezing. Chronic lung disease of infancy after premature birth, a separate entity that involves considerable developmental disturbance of the lung, becomes manifest with episodic or unremitting wheezing in the preschool years.⁷

This etiologic heterogeneity makes it difficult to interpret therapeutic trials involving preschool children. If children with wheezing are enrolled in a study, it is likely that they represent a spectrum of wheezing phenotypes. For example, if children with a first episode of wheezing are stud-



ied, their condition may represent a single viral-induced event or it may reflect the start of an unremitting disease process eventually resulting in asthma. Of course, when a child is studied, it is not possible to know whether he or she will have asthma in the future, and because of this we look for predictors of childhood asthma, such as family history of the disease, presence of atopic dermatitis in the infant,⁸ infection by rhinovirus,⁴ genetic polymorphisms,⁹ and biomarkers such as cytokines,¹⁰ level of exhaled nitric oxide,¹¹ and eosinophil counts.⁸ Even so, the predictive value of this information for the individual patient has been disappointing.

These challenges are evident in the study by Plint and colleagues¹² in this issue of the *Journal*. They enrolled children between 6 weeks and 12 months of age with a first episode of wheezing associated with signs of an upper respiratory tract infection. Since the researchers could not predict the future, some of the children in their study may have had simple bronchiolitis, whereas others may have had the first of many episodes to come. Response to treatment may, however, vary by wheezing phenotype (Fig. 1). Although children with asthma usually respond to inhaled and systemic corticosteroids, there is less evidence of such a response during the preschool years,^{13,14} when viral-induced episodic wheezing occurs more frequently. This treatment dilemma is particularly pronounced at the time of the first wheezing attack accompanied by severe respiratory distress. In such patients with bronchiolitis, epinephrine has been reported to be of short-term, but not sustained, benefit.¹⁵ In contrast, Plint and colleagues¹² showed unexpectedly that only the combination of epinephrine with an oral corticosteroid had a minimal therapeutic effect on clinical outcomes. Given the small effect size of the study — 11 infants would have to be treated to prevent one hospital admission — it does not seem practical to apply the treatment, especially considering the potential effects of high-dose corticosteroids on brain and lung development¹⁶ in such young children.

What is the best way to treat wheezing in a preschooler? Although it is essential during the first episode to provide supportive care — including supplemental oxygen, hydration, nutrition, and short-term bronchodilation — the key intervention is close follow-up. We need to assess risk

factors and symptom history and make sure that we identify and treat children with unremitting wheezing. In these children, particularly those presenting with signs of atopy, maintenance treatment can be initiated with inhaled corticosteroids, administered through an appropriate spacer, or with leukotriene-receptor antagonists.² Both can be used in combination with short-acting beta-agonists on demand. Given the variable course of wheezing over time and the lack of disease-modifying therapy options,¹⁷ a reevaluation of the patient's symptoms and history after a few weeks and a dose reduction or cessation after a few months seem justified. Modifying the treatment as it becomes clear that a child's phenotype is associated not with episodic wheezing but with unremitting wheezing (e.g., after atopy develops) makes good clinical sense. Paying attention to changes in phenotype is our best means of dealing with uncertainties in the management of preschool wheezing.

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1. Illi S, von Mutius E, Lau S, Niggemann B, Grüber C, Wahn U. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet* 2006;368:763-70. [Erratum, *Lancet* 2006;368:1154.]
2. Brand PL, Baraldi E, Bisgaard H, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008;32:1096-110.
3. Saglani S, Bush A. The early-life origins of asthma. *Curr Opin Allergy Clin Immunol* 2007;7:83-90.
4. Walton RP, Johnston SL. Role of respiratory viral infections in the development of atopic conditions. *Curr Opin Allergy Clin Immunol* 2008;8:150-3.
5. Stocks J, Devereux C. The effect of parental smoking on lung function and development during infancy. *Respirology* 2003;8:266-85.
6. Latzin P, Rössli M, Huss A, Kuehni CE, Frey U. Air pollution during pregnancy and lung function in newborns: a birth cohort study. *Eur Respir J* 2009;33:594-603.
7. Baraldi E, Filippone M. Chronic lung disease after premature birth. *N Engl J Med* 2007;357:1946-55.
8. Castro-Rodríguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403-6.
9. Vercelli D. Discovering susceptibility genes for asthma and allergy. *Nat Rev* 2008;8:169-82.
10. Copenhaver CC, Gern JE, Li Z, et al. Cytokine response pat-

terns, exposure to viruses, and respiratory infections in the first year of life. *Am J Respir Crit Care Med* 2004;170:175-80.

11. Latzin P, Kuehni CE, Baldwin DN, Roiha HL, Casaulta C, Frey U. Elevated exhaled nitric oxide in newborns of atopic mothers precedes respiratory symptoms. *Am J Respir Crit Care Med* 2006;174:1292-8.

12. Plint AC, Johnson DW, Patel H, et al. Epinephrine and dexamethasone in children with bronchiolitis. *N Engl J Med* 2009;360:2079-89.

13. Panickar J, Lakhanpaul M, Lambert PC, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med* 2009;360:329-38.

14. Ducharme FM, Lemire C, Noya FJ, et al. Preemptive use of

high-dose fluticasone for virus-induced wheezing in young children. *N Engl J Med* 2009;360:339-53.

15. Hartling L, Wiebe N, Russell K, Patel H, Klassen TP. Epinephrine for bronchiolitis. *Cochrane Database Syst Rev* 2004;1:CD003123.

16. Tschanz SA, Damke BM, Burri PH. Influence of postnatally administered glucocorticoids on rat lung growth. *Biol Neonate* 1995;68:229-45.

17. Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354:1985-97.

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